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## EDITOR'S PAGE

## Potential Effect of Brexit on Cardiovascular Translational Science

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Britain's popular vote to leave the European Union (EU), termed Brexit, could cause major disruptions for science and health care not only in the United Kingdom, but also in mainland Europe and the United States if appropriate steps to mitigate this risk are not taken. Although a number of op-ed papers have been written recently in leading medical and scientific journals on the potential effect of Brexit on science, the pharmaceutical industry, and health care, none of these papers have discussed the potential ramifications for cardiovascular translational medicine. Given that translational science requires effective cooperation between basic and clinical investigators in academia and industry, patients and their families, patient advocacy groups, and governmental funding and regulatory agencies to evaluate and develop new therapies, the global translational "eco-system" is inherently fragile and is therefore extremely vulnerable to economic and/or political turbulence. Here, we highlight several of the potential consequences of Brexit on cardiovascular translational medicine.

We believe that there are 3 potential negative consequences of Brexit with respect to cardiovascular translational medicine. The first and most obvious concern is that any financial turmoil in the United Kingdom's economy, along with a reduction in European and industrial research funding streams, may result in decreased funding for U.K. scientists. This is particularly important for translational research, which is traditionally slow and fraught with risk, but where the United Kingdom has a strong track record. If the inherent difficulties in conducting translational research become compounded by an unstable

funding climate, it may entice U.K. investigators to pursue other, more stable lines of investigation and/or funding. Further, it may dissuade trainees from pursuing basic and/or translational science in U.K. laboratories. One of the painful lessons learned in the United States from the effect of "sequestration" on the National Institutes of Health budget, is that turning the fiscal faucet back on after a period of diminished funding does not wash away the untoward consequences of closed laboratories and/or a shrunken/despised scientific work force. Any instability in funding for research has long-term consequences for science that often cannot easily be repaired, which means that progress for new therapies for patients with cardiovascular disease may be slowed, halted, or never initiated.

A second potential problem created by Brexit is the negative effect on the conduct of multinational phase II and III clinical trials and the approval process for new products. As noted by Steve Bates, CEO of the BioIndustry Association, a British life sciences trade organization, "The future structure of medicine regulation in Europe is now thrown into question" (1). The EU Clinical Trials Regulation, although not necessarily perfect, has the great advantage of establishing a common framework for clinical trials and harmonizing procedures within the EU, thereby significantly reducing the administrative burden for setting up and running multinational trials. If the United Kingdom is not within this system, then the regulation of clinical trials in Europe will require separate clinical trial authorization procedures, which will add unnecessary cost to the already expensive process of developing new therapies. Brexit may also add to the complexity of approving new therapies. As will be discussed in a forthcoming issue of *JACC: Basic to Translational Science*, the process for obtaining post-market approval differs vastly in the United States and Europe (2). Europe

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currently offers the following 4 different routes for obtaining marketing authorization for drugs: 1) a “Centralized Process” controlled through the European Medicines Agency (EMA) single license valid in all EU member states and mandatory for certain classes of drugs (treatment of human immunodeficiency virus/acquired immunodeficiency syndrome, oncology drugs); 2) a “Decentralized Procedure” in which manufacturers can apply for simultaneous approval in more than 1 EU state for products that have not yet been authorized in any EU state and do not fall under the mandatory centralized process; 3) a “National Process” in which each EU state can have its own procedures for approving drugs that fall outside of those required to undergo the centralized process; and 4) the process of “Mutual Recognition” in which drugs approved in 1 EU state via that state’s national process can obtain marketing authorization in another EU member state. If the United Kingdom is not within EU, then a separate national authorization would need to be obtained and the centralized procedure and/or mutual recognition process would not be applicable to reduce the administrative burden of applications in the EU and United Kingdom. Contrary to the common notion that Food and Drug Administration processes are significantly slower than those of the EMA, the median times for full protocol reviews are ~20% longer for the EMA compared with the Food and Drug Administration (3). Adding complexity that slows the approval process is bad for patients, and it adds costs rather than revenues for the sponsors that develop their products in Europe, which is bad for the economic engine that drives new innovations.

A third effect of Brexit on cardiovascular translational medicine is how it may influence the vitality

of the research enterprise and the “spirit of science,” both in and outside of the United Kingdom. To quote Sir Paul Nurse, a former President of the Royal Society and current Director of the Francis Crick Institute, “Science thrives on the permeability of ideas and people, and flourishes in environments that pool intelligence, minimize barriers and are open to free exchange and collaboration” (4). British translational research and medicine benefits greatly from interactions with talented scientists from across the EU and elsewhere, many of whom also come and work in the United Kingdom. The United Kingdom also has a significant effect on scientific policy decisions at the EU level. To the extent that Brexit compromises this synergistic enterprise, it has the potential to slow the scientific development of novel new therapies to treat patients with cardiovascular disease.

Much will depend upon the nature of the new relationship that is agreed between the United Kingdom and the EU. The potential risks and challenges previously discussed can be mitigated if sufficient priority is given to the maintenance and strengthening of scientific relationships. Both political will and new funding streams will likely be required. Given that cardiovascular disease remains the number 1 cause of death worldwide, we do not view Brexit as a United Kingdom or EU problem, we view it as a global problem that affects all of us. As always, we welcome your thoughts and would like to hear what you think about the effect of Brexit on cardiovascular translational science, either through social media (#JACCBTS) or by e-mail ([jaccbts@acc.org](mailto:jaccbts@acc.org)).

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